## REMARKS/ARGUMENTS

Claims 5-8 are active in this application. These claims are drawn to the elected subject matter and find support in Claim 4 and the specification as originally filed. No new matter is added.

Applicants thank Examiners Lieto and Wehbe for the courtesy of discussing this application with the Applicants' undersigned representative on February 18, 2005. During this meeting, amending the claims to define the RGD-CAP was discussed. The undersigned understood from the discussion that these amendments would cause the withdrawal of the rejections of Claim 1 and 2 under 35 U.S.C. § 112, first paragraph, the rejection under 35 U.S.C. § 112, second paragraph, and the rejection under 35 U.S.C. § 102(b). Accordingly, Applicants request that these rejections be withdrawn.

Also during this meeting, the enablement rejection was discussed. After noting the experiments provided in the specification, the Examiners requested clarification as to how these experiments, which were performed *in vitro*, correlate to an *in vivo* effect (see Interview Summary of February 18, 2005). The following is intended to address these points raised during this meeting.

Applicants note MPEP §2164.02 which states:

> If the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the Examiner has evidence that the model does not correlate.

First, the Examiner has presented no evidence demonstrating that one skilled in the art would doubt that RGD-CAP as defined in the present claims would suppress mineralization and adhesion in a patient. In the event, the Examiner could challenge the asserted utility, such a challenge would be rebutted by the significant evidence presented in the specification.

Second, the claims have been amended to define the amino acid sequence of the RGD-CAP; and the specification describes formulation on page 14, line 20; active ingredients and dosage on pages 14, lines 1-5 and the application to ligament and/or to the tooth on page 17.

Third, there is significant evidence presented in the specification which demonstrates the function of RGD-CAP in the suppression of mineralization and adhesion in the periodontal ligament. Specifically, the examples demonstrated that RGD-CAP is expressed in the periodontal ligament (PDL, see pages 23-24); and RGD-CAP negatively effects alkaline phosphatase activity in PDL cells. However, as stated on page 24, this by itself; was not entirely determinative of the ability of RGD-CAP to suppress mineralization. For this, the Applicants performed additional experiments, which demonstrated that additional mineralization markers were negatively effected (e.g., type I collagen and sialoprotein mRNAs—see page 25 and Fig. 3B) and also decreased in alizarin red staining and bone nodule formation (see page 25 and Fig. 3C).

Based on these studies alone one in the art would recognize that the *in vitro* evidence would correlate suppression of mineralization and adhesion *in vivo*. One recognizes that *in vitro* tissue culture cells have substantially the same metabolic and physiological characteristics as cells present in a whole organism and, as such, are often used to predict a efficacy *in vivo*.

Fourth, further evidence that the *in vitro* experiments correlate to an *in vivo* effect can be seen from the work presented in the Kim publication (*J Cell. Biochem.* 77:169-178 (2000))

which is of record in this case (see Applicants PTO Form 1449, reference "AU"). The report of Kim specifically identifies RGD-CAP as the gene which negatively affects osteogenesis (note that on page 1, lines 19-24, the Applicants have identified the βig-h3 described in Kim with the RGD-CAP as used in the present specification). Specifically, Kim undertook a study "to understand the mechanism for localized hypertosis and the soft tissue abnormalities observed in molerheostosis [and] determine which genes are deregulated in melorheostosis."[1] (page 170, Introduction, line 17). They obtained cells from patients and analyzed the gene expression in these cells and determined that RGD-CAP (βig-h3) is significantly reduced in the cell of the affected tissue from a patient (see page 171 and Figs. 1 and 2). Kim further determined that RGD-CAP inhibited ostogenesis (bone nodule formation) in the experiments presented in Figures 5 and 6.

While the experiments in Kim are performed *in vitro*, when assessed in view of the body of evidence provided in the present application, these data clearly demonstrate the involvement of RGD-CAP in the suppression of mineralization and adhesion *in vivo*.

Based on the foregoing, Applicants respectfully submit that the present invention is fully enabled by the disclosure provided in this application. Accordingly, withdrawal of this ground of rejection is respectfully requested.

For the foregoing reasons, it is respectfully submitted that this application is now in a condition for allowance. A notice of allowance for Claims 5-8 is earnestly solicited.

[1] "Melorheostosis is a rare bone disease characterized by linear hyperostosis and associated soft tissue abnormalities" (page 169, Abstract, line 1) and "Melorheostosis is a rare disease characterized by a "flowing" hperostosis of the cortex, resembling wax dripping down one side of a candle." (page 169, Introduction, line 1).

Should the Examiner deem that any further action is necessary to place this application in even better form for allowance, he is encouraged to contact Applicants' undersigned representative at the below listed telephone number.

Respectfully submitted,

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